LECTURE 8
UNDERSTANDING T1, T2 AND T2*
Lecture Notes by Assaf Tal

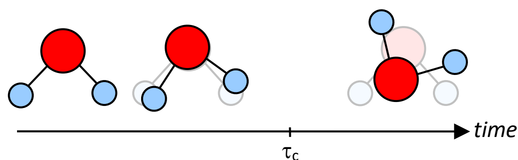
THE ORIGINS OF T1 AND T2: RELAXATION THEORY:

Spins Are Subjected To Microscopic Fluctuating Magnetic Fields Due To Their Thermal Motion

We've already remarked that spins are subjected to fluctuating fields due to their rotational thermal motion (see "Spin Dynamics" lecture). It is these fluctuating fields that lead to relaxation. The fluctuating fields $\mathbf{B}_D$ felt by a spin can be composed into components transverse & longitudinal to the main B_0 field:

$$\mathbf{B}_D(t) = \mathbf{B}_{D,\perp}(t) + \mathbf{B}_{D,\parallel}(t) .$$

It is instructive to assign some orders of magnitude to these fluctuations. We define the **rotational correlation time**, τ_c, in an informal manner as follows: imagine opening your eyes at t=0, then shutting your eyes and re-opening them at some time t>0. If we open the eyes "fast enough", you can predict that the orientation of the molecule will remain close to its orientation at t=0. However, after a certain amount of time, you will not be able to predict the orientation of the molecule at all. The time-scale at which this happens is the rotational correlation time.

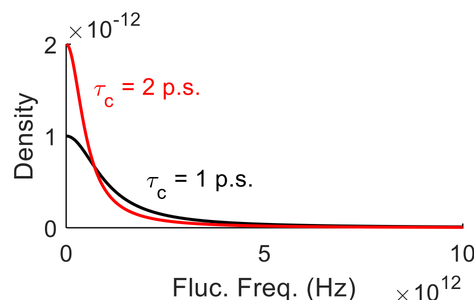


The correlation time of a molecule will depend on the temperature, its environment and its size. For a spherical molecule of hydrodynamic radius r in a liquid with viscosity η, Stoke derived an expression for the rotational correlation time:

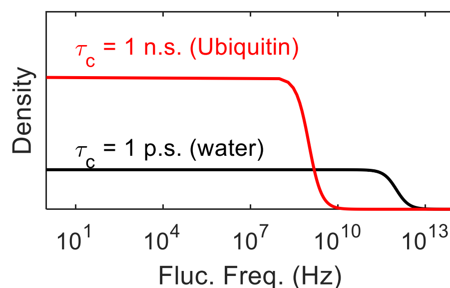
$$\tau_c = \frac{4\pi\eta r^3}{3kT} .$$

> **Number time.** For water (≈18 Da) at room temperature it is about one picosecond = 10^{-12} seconds (1 p.s.). For ubiquitin (≈9 kDa) in water, τ_c is a few nanoseconds.

Even in a liquid with a given correlation time, τ_c, there will be a distribution of the frequencies of fluctuating fields: some molecules will see slow fields, while others will see fast-fluctuating fields (with a frequency up to about $1/\tau_c$). The spectral distribution of fluctuating fields is called the **spectral density** of the fluctuations. It's very difficult to measure experimentally and it is beyond the scope of these lecture notes to offer theoretical derivations of it. However, it will typically have a general form that decays with a time constant $\frac{1}{\tau_c}$ and looks like this (drawn for two different correlation times):

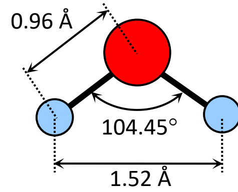


The longer τ_c, the more "bunched up" it will appear, with more slow fluctuations. Because correlation times vary by orders of magnitude between molecular sizes (from picoseconds to nanoseconds and even slower), spectral densities are often drawn on a log-log scale:



This makes them a little bit deceiving, because they seem "flat", but they in fact increase throughout.

How about the size of the fluctuations? In a water molecule the sources of fluctuations are dipolar and can be divided into intra- and inter-molecular. Because the dipolar field goes as r^{-3}, the intermolecular contributions are only a second order effect, and we are left with the intramolecular ones, exerted by one hydrogen in H_2O on the other. First, we must examine the geometry of the water molecule:



The dipolar field created by one spin at the position of the other is:

$$\mathbf{B}=\frac{\mu_0}{4\pi}\frac{3\hat{\mathbf{r}}\left(\mathbf{m}\cdot\hat{\mathbf{r}}\right)-\mathbf{m}}{r^3}$$

where **r** is the vector connecting both hydrogen atoms. We see that the maximal and minimal values of **B** occur when **m** and **r** are either parallel or antiparallel, leading to the values:

$$\left|\mathbf{B}_{\max}\right|=\frac{\mu_0 m}{2\pi r^3}$$

Hence the magnitude of the fluctuations vary between $\pm\left|\mathbf{B}_{\max}\right|$. Fixing $|\mathbf{r}|$=1.52Å and $\left|\mathbf{m}\right|=1.4\times10^{-26}\,\frac{J}{T}$ (^{1}H magnetic moment), this amounts to

$$\left|\mathbf{B}_{\max}\right|\approx 8\times10^{-4}\ T=8\,\text{Gauss}.$$

A Word About Relaxation Rates

A lot of people prefer talking about **relaxation rates**, which are the inverse of the relaxation times:

$$R_1=\frac{1}{T_1},\quad R_2=\frac{1}{T_2}$$

This is because rates tend to be additive. For example, if a proton relaxes due to both T_2 and T_2', then

$$s\ t\sim e^{-\frac{t}{T_2}}e^{-\frac{t}{T_2'}}=e^{-R_2t}e^{-R_2't}=e^{-\ R_2+R_2'\ t}$$

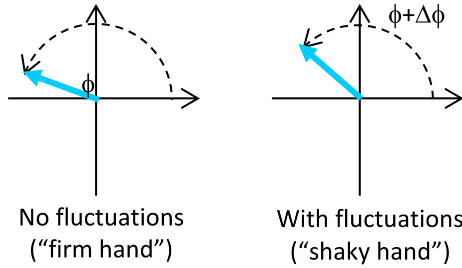
In general, uncorrelated rates will add up while times do not. Another example: If you give 1 apple a day to person A, and 2 apples a day to person B, then the total rate of apple-giving is (1+2)=3 apples/day. Relaxation just describes the rate of "giving away magnetization" for a spin, and so obeys a similar algebra.

Understanding Relaxation: Simple Solvents

The first step to understanding the effect of fluctuations on T_1 and T_2 is to think about simple solvents. For example: what happens to a water molecule with a correlation time τ_c, tumbling about and experiencing fluctuation fields? Biological systems are more complex, but understand such a simple system is an important first step. To a first approximation, as we will argue next**, the longitudinal fluctuating field causes transverse relaxation and the transverse fluctuating field causes the longitudinal relaxation**.

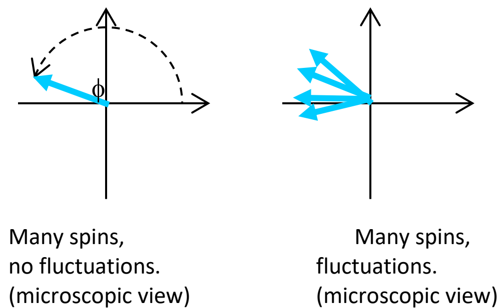
A Heuristic View: The Longitudinal Fluctuating Field Leads to T_2 Relaxation

We start by showing how a fluctuating longitudinal field leads to transverse T_2 decay. Imagine exciting a spin onto the xy plane. Without the fluctuating field, it would just execute precession and make a phase $\phi=\gamma B_0 t$ after precessing for a time t. With the fluctuating field along z the precessing frequency fluctuates as well, with the end result being a slightly different precessing frequency at the end, $\phi+\Delta\phi$, where $\Delta\phi$ depends on the exact nature of the fluctuations (imagine turning a wheel with a shaking hand):



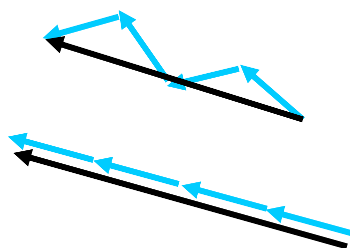
No fluctuations (“firm hand”) With fluctuations (“shaky hand”)

Now imagine a number of spins. In the absence of fluctuations they would all make the same angle. In the presence of fluctuations, they would fan out about the average position (remember, each spin feels a different temporal fluctuation):



Many spins, no fluctuations. (microscopic view) Many spins, fluctuations. (microscopic view)

This is what happens microscopically. Now, the macroscopic magnetization is the (vector) sum of the microscopic magnetization. What happens when you sum vectors that don’t point in the same direction? They (partially) cancel out. Example:



Top: Adding up slightly “out-of-phase” magnetization vectors leads to signal loss (smaller vector sum). **Bottom**: When all vectors are in-phase there is no signal loss.

You can now see why the magnetization in the plane decays:

> The fluctuating z-field causes the spins to spread out (**dephase**), and hence add up destructively, leading to a decay of the macroscopic magnetization vector, **M**.

How fast does **M** decay – what determines T_2? Quite simply: the rate of fluctuations. Fast fluctuations will result in lesser dephasing and hence slower decay.

An analogy from physics might help you see this: think of diffusion. An ink is injected into two cups containing two fluids, one denser than the other. In which cup will the ink spread further? In the *less dense* fluid. The idea is that the additional collisions it undergoes per unit time in the dense fluid slow the ink down and minimize the distance it can diffuse to at a given amount of time. A similar process occurs when discussing T_2: you can think of the spin’s phase as “diffusing” under the action of the fluctuating field – slower fluctuations mean “fewer collisions” and hence a “less dense” environment, leading to greater “diffusion” (dephasing, in our case).

T_2 Dephasing	Diffusion
Rotational motion	Translational motion
Fluctuating fields	Collisions
Spins’ phases	Translation
Fast fluctuations	Many collisions per unit time
Little dephasing / slow decay	Slow spread

This directly relates to the environment in which a spin resides. For example, free water tumbles very quickly, and as a result the T_2 relaxation times of, say, cerebrospinal fluid, can be very long – often seconds:

Free water
→ Tumble fast
→ Fast fluctuations
→ Long T_2 (slow decay)

On the other hand, inside a cell, a water molecule can get trapped inside or near a protein, which is a large molecule that rotates very slowly. Water right next to proteins forms hydrogen bonds with ions in the protein, so the protein is surrounded by a **hydration shell** (or solvation shell) that can be around a nanometer in thickness[1]. In this case:

[1] Laage et al, Chem. Rev. 117(16):10694 (2017)

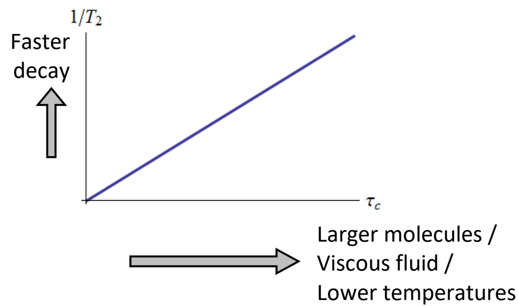
Water stuck inside/on proteins

→ Tumble slowly

→ Slow fluctuations

→ Short T_2 (fast decay)

A water molecule stuck strongly enough to a semi-solid large protein or surface, such as DNA, can experience T_2s as short as[2] 1 μs! We can draw this qualitative graph, which indicates that the relaxation rates $1/T_2$ become faster (and T_2 becomes shorter) as the correlation times become longer:



On one end of this extreme – protons in solids – motion is greatly reduced and T_2 can be extremely short. Solid-state NMR is far outside the reach of this lecture, but I'll just remark that T_2 relaxation times in solids often enter the sub-microsecond range.

A Mathematical Model for T_2

Let's assume we have fluctuating field along the z-axis, that can either point up or down with a fixed magnitude ΔB. The timescale for its fluctuations is τ, meaning every τ seconds the field reorients itself randomly and can either equal $\pm\Delta B$. We denote by

$$B_{z,1}, B_{z,2}, B_{z,3}, \ldots$$

the values of the random z-field at times 0, τ, 2τ, and so forth. A spin in the xy plane will accumulate a phase during each of these intervals:

$$\Delta\phi_1 = \gamma B_{z,1}\tau$$

$$\Delta\phi_2 = \gamma B_{z,2}\tau$$
$$\Delta\phi_3 = \gamma B_{z,3}\tau$$
$$\vdots$$

The total phase after N such time steps, at a time $t = N\tau$, is

$$\phi_N = \sum_{j=1}^{N} \Delta\phi_j = \gamma\tau \sum_{j=1}^{N} B_{z,1}$$

On average, this total phase is zero: $\langle\phi_N\rangle = 0$. However, the uncertainty of its value increases with time. This is exactly like diffusion: if you put a drop of ink in the center of a container with way, its center will remain fixed, but it will keep on expanding. We can calculate this spread, called the standard deviation, by calculating the average *squared distance* from the origin and taking the square root:

$$\delta\phi_{\ N} = \sqrt{\langle\phi_N^2\rangle}$$

Plugging in our expression for ϕ_N, we find:

$$\phi_N^2 = \gamma^2\tau^2 \sum_{j,k=1}^{N} B_{z,j}B_{z,k}$$

We make the observation that the average product of $B_{z,j}B_{z,k}$ at different times $j \neq k$ is zero: because the field reorients itself randomly at each time step, this product will sometimes be positive and sometimes negative with equal probability, so

$$\langle B_{z,j}B_{z,k}\rangle = 0 \qquad j \neq k$$

However, when j=k, this will always equal the fixed value ΔB^2:

$$\langle B_{z,j}B_{z,k}\rangle = \ \Delta\mathrm{B}^{\ 2} \qquad j = k$$

Using these observations, we can take the average over ϕ_N^2 and keep just the N elements for which j=k, which will become $\Delta B^{\ 2}$:

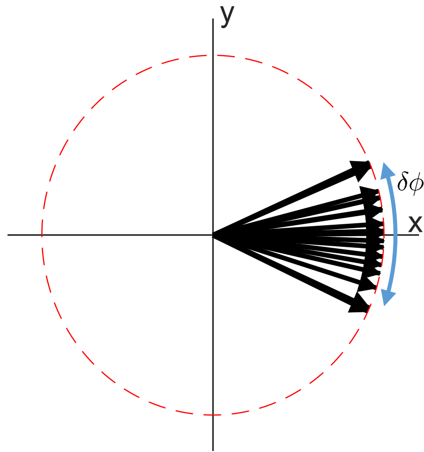
$$\langle\phi_N^2\rangle = N\ \gamma\tau\Delta B^{\ 2}$$

[2] The same reasoning applies to protons which are part of the protein itself (i.e. not water protons). However, protons in proteins contribute negligibly to the MRI signal because of their very low abundance, and will therefore not be considered here.

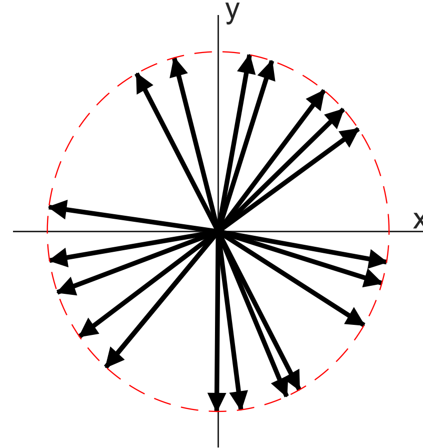
and (using $t = N\tau$):

$$\delta\phi\ \ t\ \ = \sqrt{N}\gamma\Delta B\tau = (\gamma\Delta B\sqrt{\tau})\sqrt{t}$$

What does this mean? If we take a group of spins in the transverse plane, all starting out from the x-axis – let's say, 15 spins – and subject each to a different fluctuating z-field, then they will end up accumulating different phases after a time t. The angular "width" of this distribution will be given by $\delta\phi(t)$ (neglecting T_2 relaxation):



If you wait for long enough, the spins will completely and randomly occupy all directions in the transverse plane, effectively canceling each other out and result in zero signal:



This dephasing leads to the signal decay associated with T_2 relaxation. We can use our model to estimate the value of T_2 from the "microscopic" parameters characterizing our fields. Signal decay will occur at a time T_2 such that the spread is on the order of half a circle (when it's a full circle the signal will have decayed to zero completely, surpassing T_2):

$$\delta\phi\ \ T_2\ \ \sim\pi$$

That is:

$$T_2\sim\frac{\pi}{\gamma\Delta B\ \ ^2\tau}$$

Does this make sense? First, dimensional analysis confirms this has units of time. But what about the order of magnitude? As I've stated, τ is given by the rotational correlation time. For a water molecule[3] rotating in distilled water and at room temperature,

$$\tau\sim 2\cdot 10^{-12}\ \mathrm{sec}$$

The size of the magnetic field is obtained by taking the dipolar interaction between two protons in a water molecule. This was estimated above to be:

$$\Delta B\sim 8\ \mathrm{Gauss} = 8\cdot 10^{-4}\ \mathrm{T}$$

Putting it all together, along with $\gamma = 2\pi\cdot 42.576\cdot 10^6\,\frac{\mathrm{Hz}}{\mathrm{T}}$, we obtain:

[3] See D. Lankhorst et al, Berichte der Bunsengesellschaft für physikalische Chemie, 86(3):215-221 (1982)

$$T_2 \approx 22 \text{ sec}$$

The T_2 of distilled water at room temperature tends to be on the order of a few seconds, so we're off by a bit but our model makes sense and is, in fact, in-line with more advanced models which improve on it but retain its basic ideas. Those models yield extremely good agreement for simple solvents, and were pioneered in the 1940s by Bloembergen, Purcell and Pound – hence the name of their theory: **BPP theory**[4].

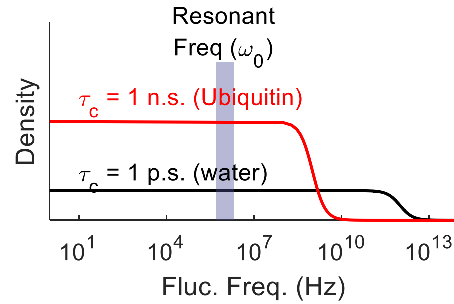
Our simple model also tells us that T_2 should be independent of B_0.

The Transverse Fluctuating Field Leads to T_1 Relaxation

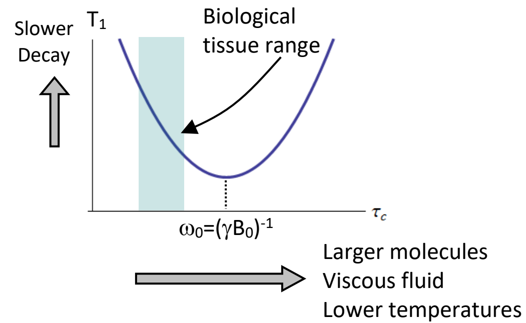
Remember one of our earliest questions when discussing relaxation: how can it be that a tiny RF component compared to B_0 can excite the spins? The answer we found is that a weak RF field can excite the spins if it is on resonance. We can reverse the reasoning and state that **a transverse fluctuation will appreciably affect to z-component of the spins if it is resonant**.

If we think of the transverse fluctuating field in terms of its frequency components, we might imagine that when $\tau_c \sim \frac{1}{\gamma B_0}$ – that is, when the timescale of the fluctuations is on resonance – the longitudinal relaxation will be most effective, leading to the shortest possible T_1. Conversely, as τ_c becomes slower or faster than $1/(\gamma B_0)$, we can predict that it will be less effective at inducing longitudinal relaxation, leading to longer T_1s.

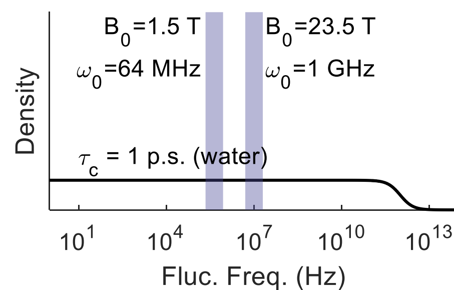
Let's think about this in terms of spectral density functions. Say we have a ubiquitin molecule and a water molecule both in a water medium, in a 3T magnet. This means that the protons in both will resonate at ~127 MHz, and that fluctuating fields at around 127MHz will contribute most to their T_1 relaxation.



There are more ubiquitin molecules which experience fluctuating fields at around 127 MHz, which means their T_1 will be **shorter** than the T_1 of water molecules. T_1 will continue shortening until the molecules tumble so slowly that their spectral density has no component around ω_0. Therefore, T_1 will have the following general behavior as a function of correlation time:



We can ask ourselves another question: How does T_1 vary for a given molecule (with a given τ_c) in different field strengths B_0? This corresponds to moving the resonant frequency:



Remember that even though it appears almost constant on a log-log plot, the spectral density function increases as the frequency becomes

[4] See Bloembergen, Purcell and Pound, Relaxation effects in nuclear magnetic resonance absorption, Phys. Rev. 73, 679 (1948)

slower. Therefore, there are more water molecules which "see" microscopic fluctuating fields at 64 MHz compared to 1 GHz and, consequently, T_1 relaxation will be more effective (i.e. shorter T_1) at lower fields. In other words: **T_1 becomes longer as B_0 increases, albeit not drastically**.

Interim Summary: What Simple Relaxation Theory Tells Us, And What it Gets Wrong in Biological Tissue

The above models and corresponding theory (BPP) work well for relaxation in simple homogeneous liquids and for protons. Even the original BPP paper from 1948 shows several highly convincing applications of BPP theory using water-glycerin solutions to control τ_c. However, BPP theory only roughly explains relaxation in biological tissue. Here are some things it gets right and wrong:

1. **Wrong**: For non-proton nuclei, such as ^{31}P, T_1 relaxation time actually decreases with increasing B_0. This is because dipolar fluctuations are not very large for phosphorous nuclei. Rather, another physical relaxation mechanism, called chemical shift anisotropy, is the main source of relaxation, and it behaves differently from dipolar fluctuations which we focused on. However, let's put non-protons aside for the rest of this chapter.
2. **Right**: T_1 indeed gets longer at higher fields. For water[5], it increases approximately as $B_0^{\frac{1}{3}}$.
3. **Wrong**: Our model[6] predicts that T_2 should not change with B_0, but T_2 changes are observed, mostly as (non-drastic) T_2 reductions. For example, de-Graaf et al[7] shows that T_2 of water in the rat brain from approximately 60-75 ms at 4.0 Tesla to around 35-45 ms at 9.4 Tesla, and further still to around 30-40 ms at 11.7 Tesla.
4. **Wrong**: Although we didn't develop the full BPP theory, one of its predictions is that for fast rotating molecules (i.e. $\tau_c \ll \omega_0^{-1}$, as is the case for water), T_1 should equal T_2. This is definitely **not** observed in-vivo, where T_1 is on the order of seconds, while T_2 is on the order of tens of milliseconds (and, in some compartments, even shorter).

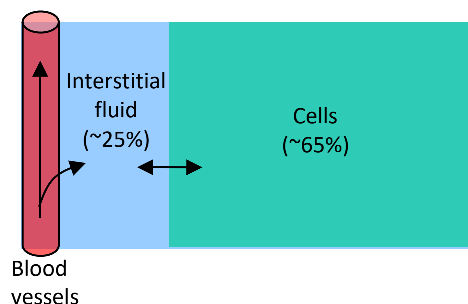
BPP theory works quite well for simple solvents, but it somewhat fails in biological tissue. Our next step would be to explain **why**.

Relaxation in Biological Tissue

Thinking in Terms of Compartments

Biological tissue can be divided into many different compartments.

1. **Macroscopic compartments**: For example, a single voxel will likely contain some blood vessels, which exchange with the interstitium. The interstitium constitutes about 25% of the body's total fluids (cells contain another two thirds, and the remainder is allocated to blood vessels and cerebrospinal fluid). The water in the interstitial fluid then exchange with cells:



2. **Microscopic "compartments"**: Now consider a water molecule inside a cell. The water molecule might spend some of its time[8] in the hydration shell of a large protein

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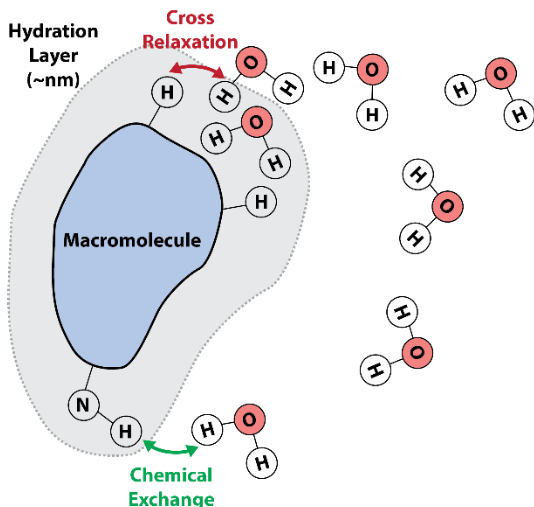
[5] See Rooney et al., Magnetic field and tissue dependencies of human brain longitudinal 1H2O relaxation in vivo, Magn Reson Med. 57(2):308 (2007)

[6] To be fair, BPP theory does predict some B_0 dependence in T2, but this dependence only becomes non-negligible in solids, where T2 is supposed to (slightly) increase with B_0. So BPP theory obviously gets this very wrong.

[7] Robin de Graaf et al, High magnetic field water and metabolite proton T_1 and T_2 relaxation in rat brain in vivo, Magn Reson Med 56(2):386 (2006)

[8] How long does a water molecule stay in the hydration shell before "wandering away"? Otting et. al. (Science, 254(5034):974-950, 1991) has shown this to be in the sub-nanosecond scale using NMR. Later studies using fast femtosecond optical spectroscopy have refined this to be in the pico-nanosecond range (see Zhong et al, Chem. Phys Lett.

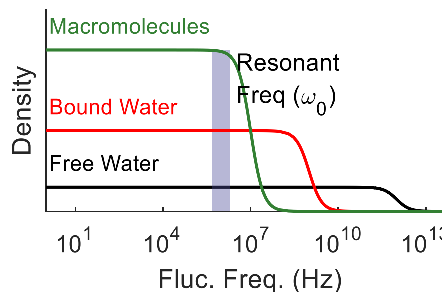
molecule (short T_2), and some of the time detached and tumbling more freely (longer T_2). The transition between environments happens very fast, on the sub-nanosecond range – much faster than T_2.



Let's think about the microscopic compartments, and about the "life of water" within a cell. For the purposes of relaxation theory, we can think of a cell as a suspension of macromolecules within a water medium (since a cell is about 60-80% water). Water protons close to a macromolecule are affected by it in three ways:

1. **Slower tumbling in hydration layer**: First, some water molecules will enter the hydration layer via diffusion, which will alter their tumbling rate. Water molecules in the hydration layer will have longer correlation times τ_c.
2. **Chemical exchange**: Some water protons will *physically* exchange with protons that are weakly attached to the macromolecule. For example, protons attached to nitrogens (N-H bonds) tend to easily detach and exchange. These rates tend to range from "slow" (a few tens of Hz) to "medium" (a few tens of kHz). Once attached to a large macromolecule the correlation time τ_c of those protons reduces drastically.
3. **Magnetization Transfer**: This is a process by which the magnetization between spatially adjacent protons becomes correlated, most often via dipolar interactions. The magnetization itself – not the proton – "hops" between the water molecule's proton and the macromolecule's proton. This mechanism happens through space, and is sometimes called **cross-relaxation**. Both magnetization transfer and chemical exchange are two very distinct processes, but are thought of the same conceptually, since both lead to a transition of magnetization from one pool to another.

In terms of the spectral density function, the protons can be found in any of these three pools, with very different correlation times:



Proton magnetization in large macromolecules has a very short T_2 and decays very rapidly after excitation (often within tens of microseconds). It is rarely directly observed. Similarly, T_1 relaxation is very efficient in macromolecules, which have a long τ_c, but not too long so as to be below the resonant frequency: $\tau_c^{-1} > \omega_0$. Therefore, BPP theory suggests for each compartment:

$$T_{2,free} \gg T_{2,bound} > T_{2,macro}$$
$$T_{1,free} \gg T_{1,bound} > T_{1,macro}$$

Biological Relaxation is Dominated by Fast Exchange[9]

Now that we've roughly described the "compartments" in biological tissue, it is obvious that *some* protons will reside in the free pool; some in the "bound" pool; and some will exchange with macromolecules.

1. **Slow exchange**: In this scenario, the protons in each compartment don't cross over. This,

503:1-11 (2011)). Trapped water inside proteins has residence times in the 10^{-2}-10^{-8} sec. range.

[9] The use of the word "exchange" here has nothing to do with chemical exchange, but rather with the fact that protons can transition ("exchange") between different compartments in our model.

for example, might be the case if water molecules diffuse very slowly, such that a free water molecule starts out and rarely encounters a macromolecule throughout excitation and acquisition.

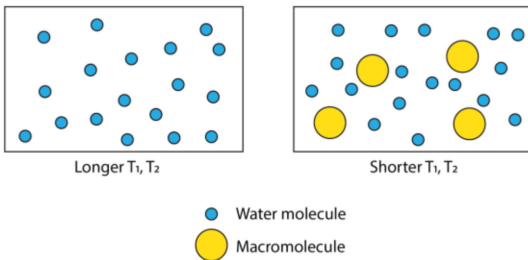
2. **Fast exchange**: Here the water molecules exchange rapidly between the different compartments. A free water molecule will encounter a macromolecule and possibly exchange magnetization with it.

Experimental data heavily supports the second, fast-exchange world view[10]. In such a case we would label by f_{free}, f_{bound} and f_{macro} the fractions of protons within each environment, such that $f_{bound}+f_{free}+f_{macro}=1$. The resulting T_2 and T_1 relaxation times would be the weighted average over all compartments:

$$\frac{1}{T_2} = \frac{f_{free}}{T_{2,free}} + \frac{f_{bound}}{T_{2,bound}} + \frac{f_{macro}}{T_{2,macro}}$$

$$\frac{1}{T_1} = \frac{f_{free}}{T_{1,free}} + \frac{f_{bound}}{T_{1,bound}} + \frac{f_{macro}}{T_{1,macro}}$$

A quantity such as f_{bound} will be proportional to the total protein content in the water molecule's environment, or, more accurately, the fraction of time a water molecule will remain in the solvation shell of a protein as it diffuses along in a cell; similarly for f_{free} and f_{macro}. Our model predicts that T_2 and T_1 are expected to be shorter when more macromolecules/proteins are present in the tissue:



Macromolecules act as "sinks"

Even small values for f_{bound} or f_{macro} can drastically alter T_1 and T_2, because macromolecules act as "sinks": a proton that comes in contact with a macromolecule relaxes very rapidly, even if it spends a small amount of time next to it. You can also see this numerically: let's take $f_{free} = 0.8$, $f_{bound} = f_{macro} = 0.1$, and $T_{1,free} = 2$ s, $T_{1,bound} = T_{1,macro} = 0.1$ s. Then:

$$\frac{1}{T_1} = \frac{0.8}{2000} + \frac{0.1}{100} + \frac{0.1}{100} \approx 0.0024 \text{ kHz}$$

which leads to

$$T_1 = 416 \text{ ms}$$

So, despite having only 20% of the water molecules around macromolecules, T_1 gets reduced drastically from ~2000 ms to 416 ms.

Why T_1 and T_2 Are Different In-Vivo.

Simple BPP theory predicts that in simple liquids T_1=T_2, which is in fact usually observed in practice. In-vivo, however, they are quite different: typical in-vivo T_1s are on the order of a second, while T_2s are on the order of several tens of milliseconds. Our picture above also explains the vast difference in T_1 and T_2: This is a result of the macromolecular magnetization being in a semi-solid state. Remember that regular BPP theory predicts (correctly) that solids and semi-solids have T_2s that are much shorter than their T_1s, because T_1 relaxation become ineffective when a macromolecule rotates very slowly. Hence,

$$T_{1,macro} \gg T_{2,macro}$$

As a result, macromolecules act as "sinks" but are much more efficient when it comes to T_2 relaxation compared to T_1 relaxation. In other words, for the same example as above which gave us T_1=416 ms, let's put $T_{2,free} = 2$ s, $T_{2,bound} = T_{2,macro} = 0.01$ s, so:

$$\frac{1}{T_2} = \frac{0.8}{2000} + \frac{0.1}{10} + \frac{0.1}{10} = 0.02 \text{ kHz}$$

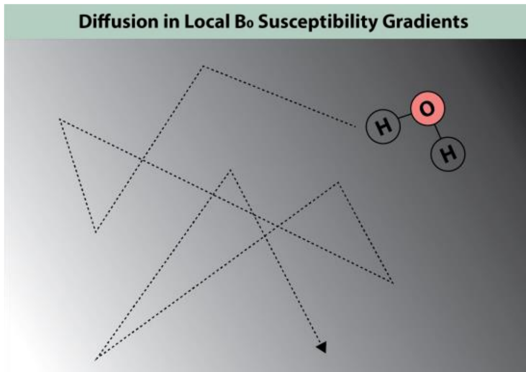
such that:

$$T_2 = 50 \text{ ms}$$

[10] Many studies support such a model for T_2 relaxation inside cells. See, e.g., Cole et al, Magn Reson Med 29(1):19-24 (1993)

Why T_2 Changes with B_0

Our world-view above *still* does not explain by T_2 should decrease with B_0. The explanation for this is given by the diffusion of water molecules across microscopic (sub-cellular-level) local susceptibility gradients[11]. As a water molecule diffuses through such a gradient, its offset changes, because its position changes and B_0 is position-dependent! This creates temporal fluctuations in B_0, akin to the field fluctuations induced by dipolar relaxations. These fluctuations are slow compared to the dipolar fluctuations due to molecular rotation, but are sometimes "fast" in the sense that they happen on timescales which are usually faster than ~ ms, and therefore cannot be refocused by 180° pulses (this is because a spin-echo assumes the offset is constant before and after the 180° pulse). In theory, if we could pulse on timescales faster than ~ ms we could refocus this component, but we can't due to hardware and SAR constraints in-vivo.

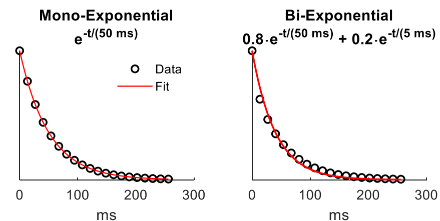


This theory explains why T_2 decreases when B_0 is increased: the local susceptibility gradients increase when B_0 increases, because it is a diamagnetic effect: as B_0 increases it induces larger diamagnetic shielding currents which in turn lead to more inhomogeneous local fields.

This discussion shows that static B_0 inhomogeneity (which often leads to T_2' relaxation) can introduce fluctuating fields **if** the water molecule *diffuses* in it. These fluctuations, although slow compared to the ones induced by molecular tumbling, still induce T_2 relaxation effects and (if the diffusion is fast enough) cannot be refocused by a 180° pulse.

Compartmentation Effects

Our picture above used a fast-exchange model to explain several features of T_1 and T_2 relaxation. However, it is also true that the environment within the voxel contains **compartments** which are separate from each other, and might or might not exchange. For example, in the central nervous system, about 10% of water molecules are trapped inside the **myelin sheath** that surrounds neurons, unable to escape[12]. This means that the signal from a white matter voxel will exhibit **multi-exponential decay**.



Left: Computer-generated mono-exponential data and an excellent corresponding monoexponential fit. Right: Bi-exponential data and a reasonable but imperfect monoexponential fit.

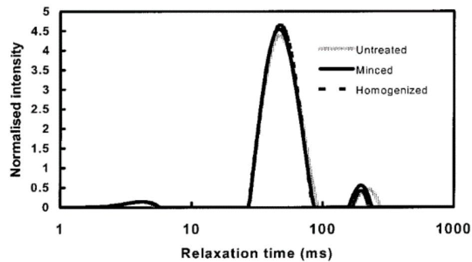
Most multiexponential decays are very difficult to tell apart visually from simpler monoexponential decays, but mathematical analysis methods confirm this behavior for many biological tissues. **The interpretation of this behavior is usually that there are two distinct pools with different T_2s (or T_1s) that do not interact; therefore, the signal is the sum of the two signals**.

When multiexponential behavior is observed in tissue it is not always simple to explain it, and each tissue type requires its own analysis and research. We give two concrete examples.

[11] See, e.g., Michaeli et al, Magn Reson Med 47(4):629-633 (2002)

[12] Ortiz et al, Magn Reson Med 73(1):70-81 (2015)

1. **Multiexponential T_2 decay in excised pork muscle:** This work at low fields (0.47 T), yielded a histogram of T_2 values the form[13]:



   The histogram showed little variation when the muscle was minced or homogenized, indicating the different T_2 pools did not originate from extra/intracellular compartments. Following further experiments, the authors showed that the fastest component (~ few percent) originates from water bound to macromolecules; the largest peak corresponds to water located within organized protein structures; and the fastest peak (longest T_2) reflects extra-myofibrillar water (i.e. between the fibers of the muscle).
2. **Multiexponential T_2 decay in WM measurements:** Here the compartments are thought to be a water fraction trapped within myelin sheaths (ca. 10-20% of all water molecules) and intra/extracellular water which are subjected to the "usual" interactions with macromolecules. The fraction of signal with a short T_2 relaxation time correlates with histological measures of myelin content[14] (typical R^2 is about 0.5).

The analysis of multiexponential decay becomes even more complicated when we consider exchange between compartments. For example, water trapped between myelin sheaths can escape into the cell at a rate that depends on the thickness of the myelin sheath. For thin enough sheaths – e.g., the rat optic nerve (0.3 μm myelin thickness) – the relaxation is predicted to be on the order of several tens of milliseconds, which is on the order of many T_2 measurements[15].

[13] Taken from Bertman et. al., J. Agric. Food Chem. 49:3092-3100 (2001)
[14] Van der Weijden, Neuroimage 226(1):117561 (2021)
[15] Dortsch et al, Magn Reson Med 70(5):1450-1459 (2013)

Using Relaxation Theory

T_1 and T_2 Both Increase in Edema

Let's take the relatively simple case of edema[16]. In edema, water accumulates in the interstitium, which constitutes about 25% of the body's total fluids (cells contain another two thirds, and the remainder is allocated to blood vessels and cerebrospinal fluid).

Both T_1 and T_2 tend to increase in edema. When you think of edema, the additional water tends to reduce the viscosity in the interstitial space, leading to a shorter correlation time, which – looking at the graphs of T_1 and T_2 – leads to an increase in both.

$T_{1,CSF}>>T_{1,GM}>T_{1,WM}$

Our theory also explains why the longitudinal relaxation times behave as they do in tissue. First, CSF is pretty much "water" with a few solvents, and its T_1 and T_2 relaxation times are long and on the order of seconds, because there is practically no macromolecular pool. It is well documented[17] that WM has a larger macromolecular mass fraction compared to GM, and our model indeed predicts that as f_{macro} increases, T_1 and T_2 become smaller. This is indeed observed in practice: R_1 correlations very well with 1/(fraction of water within a voxel), and is indeed shorter in WM compared to GM (and both are shorter than CSF).

Relaxation Properties of Blood

Relaxation times can be tied to important physiological parameters of blood. The accepted model of T_2 in the blood is[18]:

$$\frac{1}{T_2} = A + B \cdot \; 1 - Y \; + C \cdot \; 1 - Y \; ^2$$

where Y is the oxygenation fraction of the blood, and A, B and C are constants that depend on the hematocrit (volume percentage of red blood cells). Generally, both T_1 and T_2 tend to *increase* with increasing oxygenation levels and *decrease* with higher hematocrit levels[19]. Once properly calibrated, such measurements can for example

[16] In Hebrew: בצקת.
[17] e.g., Gelman et al, Magn Reson Med 45(1):71-79 (2001)
[18] Golay et al, Magn Reson Med 46(2):282-291 (2001)
[19] Liu et al, Magn Reson Med 75(4):1730-1735 (2016)

be used to measure oxygenation levels in neonates.

The physical mechanisms behind the hematocrit and oxygen level dependence are as follows: deoxygenated blood cells are paramagnetic, while oxygenated blood cells are diamagnetic. This leads to the concept similar to the one discussed above for T_2: as water molecules diffuse in an environment with an inhomogeneous B_0, they experience a fluctuating field which leads to relaxation. This has the effect of decreasing T_2 and T_1. Thus:

1. As the oxygenation level increases, blood cells become more diamagnetic and relaxation becomes more inefficient, leading to longer T_1 and T_2.
2. As hematocrit increases (for a fixed oxygenation level), more blood cells occupy the volume and lead to a more inhomogeneous environment.

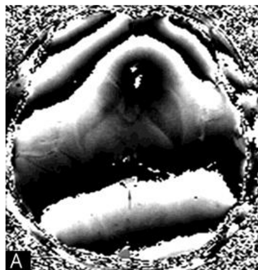
Using T_2* Contrast

In the previous Lecture we discussed the microscopic underpinnings of T_2*: B_0 spatial and static inhomogeneities.

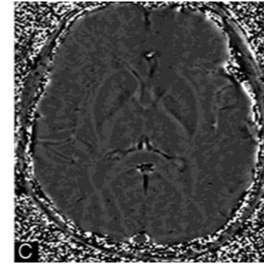
Phase Imaging Reveals Microstructure Due To Microscopic Susceptibility

As seen before, susceptibility artifacts can lead to the signal being a complex quantity. Instead of looking at **magnitude images**, we can try looking at **phase images**, that is plot the phase of the signal as each point. This might tell us something about the microstructure that created it.

When acquiring phase images, one usually gets something that looks like this (images taken from Haacke et. al., AJNR 30:19-30 (2009)):

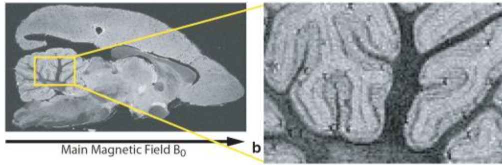


The gross variations are due to macroscopic inhomogeneity effects such as the main field's imperfections. They can be addressed by **unwrapping** the phase (canceling out its discontinuities). Once this is done, we assume that the slowly changing components of the inhomogeneity are caused by macroscopic fields, and we can get rid of them by applying a **high pass filter** which assures us we remain only with the fast changing – hopefully microscopic – parts of the phase:

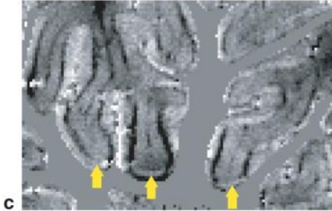


We can indeed see some contrast here between the different tissue types and also some vessel-related contrast, as will be discussed below. Indeed, by multiplying the phase and magnitude images we can get what's known as a **susceptibility weighted image**. Such images usually show better contrast for some structures, such as blood vessels, or iron-containing structures, which are known to create microscopic susceptibility artifacts around them. For example, Shmueli et. al. have examined the cerebellum in a marmoset brain at 11.7 Tesla. In humans, the cerebellum appears almost as a separate structure attached to the base of the brain, which is involved in coordinating a great deal of our motor activity. Shmueli et. al. have been able to delineate the purkinje cell layers in the marmoset brain[20]:

[20] Shmueli et al, Magn. Reson. Med., 62:1510-1522 (2009)



Left: Simple gradient-echo MR image (magnitude). Right: zoomed in cerebellum.



The phase of the above image (following unwrapping and high pass filtering), clearly showing the purkinje cell layers with high contrast.

The contrast between the different cell layers in the cerebellum is highly correlated to their **iron content** (iron particles have a large electronic magnetic moment and induce significant field distortions on a microscopic scale).

Rethinking the Spin Echo: What is the Difference Between T_2 and T_2*?

We've presented T_2 are stemming from microscopic temporal field fluctuations, and T_2' as stemming from static spatial inhomogeneities. What would happen if we created a static inhomogeneity but let a water molecule diffuse (translationally, not rotationally!) through it? The field the molecule would "see" would fluctuate as it would move around. If the molecule moves around fast enough, T_2' would "become" T_2!

This is not a hypothetical situation and it happens often in tissue. For example, water can diffuse around a blood vessel (venous blood has deoxygenated hemoglobin which is paramagnetic). These effects play a big role in undersanding hemodynamic effects in functional imaging.

One way to think about T_2' vs T_2 is as follows: imagine running a spin-echo experiment. Whatever the spin-echo keeps is T_2, and whatever goes away is T_2'.